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Remarks

Claims 1, 2, and 4-6 are currently pending in the application. In order to advance prosecution, Applicants have amended claim 1. A complete listing of all the claims, in compliance with the revised amendment format, is shown above. The amendments to the pending claims are made in order to expedite the issuance of the claims. The amendments are made without prejudice, do not constitute amendments to overcome any prior art rejection, and do not present any new matter.

Applicant gratefully acknowledges the Examiner's withdrawal of the rejection under 35 U.S.C. § 112 set forth in the previous Office Action.

Discussion of the 35 U.S.C. § 112 Rejection(s)

Claims 1, 2, and 4-6 stand rejected under 35 U.S.C. § 112 as failing to comply with the enablement requirement, based on the following reasons: (1) there is no correlation between TGF-ß, p21, p16, and p27 and the states of apoptosis, terminal differentiation, and senescence within a "tissue or cell sample" treated by a chemotherapeutic agent; (2) the term "chemopreventive" agents is not enabled; and (3) the specification does not teach the use on an antibody in staining SA-ß-Gal. Applicant respectfully addresses each ground of rejection in turn.

With respect to the reason for rejection (2), that the term "chemopreventive" agent is not enabled, the Office Action stated that the neither the specification nor the prior art teaches the administration of a chemopreventive agent to and individual and the removal of cell or tissues from said individual for the determination of an increase in SA-ß-Gal, p21, p27, p16, or TGF-ß. Although not acquiescing to this ground of rejection, and merely in an effort to expedite issuance

of the claims, Applicant has amended the claim to remove this limitation. Applicant respectfully contends that the claim amendment has overcome the asserted ground of rejection.

With respect to the reason for rejection (3), that the specification does not teach the use on an antibody in staining SA-ß-Gal, the Office Action stated that the specification does not contemplate the measurement of levels of SA-ß-Gal by means of an antibody. Although not acquiescing to this ground of rejection, and merely in an effort to expedite issuance of the claims, Applicant has amended the claim to remove this limitation. Applicant respectfully contends that the claim amendment has overcome the asserted ground of rejection.

With respect to the reason for rejection (1), that there is no correlation between TGF-ß, p21, p16, and p27 and the states of apoptosis, terminal differentiation, and senescence within a "tissue or cell sample" treated by a chemotherapeutic agent, the Office Action stated that given the breath of claims to encompass any sample of tissue or cells taken from an individual who has received a chemotherapeutic agent, and the lack of a correlation between the increased expression of the aforementioned markers and a therapeutic effect, one of skill in the art would be subject to undue experimentation in order to practice the claimed method. Applicant respectfully traverses this ground for rejection.

The instant claims are drawn to methods of determining a response to administration of a cancer chemotherapeutic agent to an individual comprising, *inter alia*, determining whether the expression of one or more of p21, p27, p16, TGF-ß, or SA-ß-Gal are increased in a tissue or cell sample from an individual after exposing the individual to the cancer chemotherapeutic agent as compared to a tissue or cell sample collected from the individual before exposing the individual to the cancer chemotherapeutic agent. Applicant respectfully submits that this ground of rejection is based on the incorrect premise that a decrease or lack of change in the expression of

p21, p27, p16, TGF-ß, or SA-ß-Gal in response to a cancer chemotherapeutic agent is relevant to the claims. Instead, the claims are not drawn to making any determination based on a decrease or lack of change in the expression of any biological marker following exposure of an individual to a cancer chemotherapeutic agent, especially p21, p27, p16, TGF-ß, or SA-ß-Gal. In other words, situations where these markers are decreased or not changed in response to exposure to a cancer chemotherapeutic agent are outside the scope of the amended claims.

To support this ground of rejection, the Office Action cites to several references that describe biological situations where the expression of p21, p27, p16, TGF-ß, or SA-ß-Gal is unchanged or decreased in tissue or cell samples after the sample or the individual from whom the sample was collected was exposed to a cancer chemotherapeutic agent. However, again, these examples are irrelevant to the pending claims. For example, the Office Action cites to Morris *et al.* as teaching that the treatment of Raji lymphoma *in vivo* with methylprenisolone did not change the level of observable TGF-ß, and that p21 was decreased. Also, the Office Action cites to Urashima *et al.* as teaching that the p16 gene is frequently deleted in lymphoblastic leukemia associated with growth of less differentiated tumor cells. Obviously, as the Office Action acknowledges, when the p16 gene is truly deleted, the level of p16 will not increase in response to any agent. Wang *et al.* is cited as teaching that cisplatin induced a senescence-type growth arrest in human tumor cell lines, with no change to either the level of p16 or p21. Sethi *et al* is cited as teaching that the expression of Bcl2 in lymphomas confounds the apoptosis-inducing affect of TGF-ß, and therefore, the Office Action concludes, detection of increased TGF-ß would not be indicative of apoptosis. Sethi did, in fact, report the observation of the *presence* of TGF-ß in patient samples contained bcl-2 but were non-apoptotic. However, these observations were made *before* the samples or the individuals were exposed to a cancer

chemotherapeutic agent. Thus, none of these examples are relevant to claims for determining whether the expression of one or more of p21, p27, p16, TGF-ß, or SA-ß-Gal are *increased* in a tissue or cell sample from an individual *after* exposing the individual to the cancer chemotherapeutic agent as compared to a tissue or cell sample collected from the individual *before* exposing the individual to the cancer chemotherapeutic agent.

Moreover, the Office Action argues that it would be necessary to assay for the expression of p21, p27, p16, TGF-ß, or SA-ß-Gal within a set period of time, because it would be necessary to determine the time frame of apoptosis induction by means of observing DNA strand breaks before proceeding to determine if one or more of the markers were increased. In support, the Office Action cites Li *et al* as teaching that apoptosis was seen between 8 to 24 hours after the administration of DNA topoisomerase inhibitors, but 48-72 hours after the administration of Taxol or Ara-C. The Office Action also argues that it would be necessary to determine the dose at which the agent causes apoptosis, and cites the abstract of Cen *et al.* for the proposition that at certain dosages, chemotherapeutic agents are insufficient to cause apoptosis. However, the Office Action is clearly reading limitations into the claims. In both of these cases, if the timing after administration or the dosage of a cancer chemotherapeutic agent were insufficient to determine whether expression of p21, p27, p16, TGF-ß, or SA-ß-Gal was increased, it would not fall within the scope of the claims. As already stated, the claims do not cover situations in which a decrease or lack of change in the expression of p21, p27, p16, TGF-ß, or SA-ß-Gal in response to a cancer chemotherapeutic agent is observed. Thus, a need to determine the timing of the onset of apoptosis after administration of a cancer chemotherapeutic agent or the determination of dosage of the agent is simply not required to practice the claimed invention.

Finally, the Office Action cites three further situations in support for this ground of rejection. However, as above, these situations are irrelevant to the pending claims. Cohen *et al.*, Bacus *et al.*, and Chang *et al.* are cited as teaching that the induction of p21 in breast cancer cell lines in response to doxorubicin fails to occur in cells expressing mutated or dominant negative p53. Chang *et al.* (ff) is cited as teaching that the chemotherapeutic induction of a senescence-like phenotype versus the induction of cell death in human tumor cell lines is independent processes. However, it is silent to whether a response to administration of a cancer chemotherapeutic agent can be identified by determining the expression of p21, p27, p16, TGF-ß, or SA-ß-Gal following exposure to the agent. Finally, Eymin *et al.* is cited as teaching that over-expression of p27 is indicative of drug resistance in leukemic cells. However, not only is p27 overexpression seen both before and after administration of the agent, likely resulting in an observation of no change of the marker, but Eymin reports that the cells *still* undergo apoptosis, albeit in a delayed manner, *see* Eymin, pg. 1412 and fig. 1. Therefore, none of the art cited by the Office Action is relevant to the claimed invention of determining a response to administration of a cancer chemotherapeutic agent to an individual comprising, *inter alia*, determining whether the expression of one or more of p21, p27, p16, TGF-ß, or SA-ß-Gal are increased in a tissue or cell sample from an individual after exposing the individual to the cancer chemotherapeutic agent as compared to a tissue or cell sample collected from the individual before exposing the individual to the cancer chemotherapeutic agent.

For the reasons set forth above, none of the references cited in support of this ground of rejection establish that the claims are not enabled based on a supposed lack of correlation between TGF-ß, p21, p16, and p27 with the states of apoptosis, terminal differentiation, and senescence within a tissue or cell sample treated by a cancer chemotherapeutic agent.

Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection and pass these claims to issue.

Conclusion

In view of the above amendments and remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully Submitted,

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